‘‘FORMULATION AND CHARACTERIZATION OF POORLY WATER-SOLUBLE DRUGS BY USING SOLID DISPERSION TECHNIQUE’’

A SYNOPSIS

Submitted for the consideration of

Registration for the Degree of *Doctor of Philosophy*

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By

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1. AIM & OBJECTIVES:

The aim of present study is formulation and characterization of poorly water soluble drugs by solid dispersion technique.

OBJECTIVES

The present study is designed with the following objectives:

1) Preformulation studies to find out the compatibility between the drug and the polymers by FT-IR spectroscopy and DSC.
2) Evaluation of drug delivery strategy for poorly water soluble drugs.
3) Preparation of solid dispersion by suitable technique.
4) Formulation of solid dispersion formulations.
5) Characterization of solid dispersion by various tools
    a. Physical characterization
    b. Chemical characterization
    c. In-Vitro drug release studies
    d. Stability study of optimized best formulation.

2. INTRODUCTION:

The advances in automated synthesis, combinatorial chemistry and innovative high-throughput screening have led to the production of a vast number of potential drug candidates, as well as introducing more poorly water-soluble drugs in the pharmaceutical pipeline. It is estimated that > 40% of marketed drugs are poorly water-soluble (1, 2); among the US pharmacopeia, this share is > 30% (2) for the drugs exhibiting low solubility but reasonable membrane permeability. These are categorized as BCS class II, the rate-limiting process of absorption is the drug dissolution step. Formulation plays a major role in determining the rate and extent of absorption of such drugs from the gastrointestinal tract. The bioavailability from conventional tablet formulations may be unacceptable for these drugs, which often have water-solubility of < 1 μg/ml (3). A number of formulation strategies have been developed to improve the delivery of BCS class II drugs. They are based on either techniques to increase the drug dissolution rate or techniques to achieve sustained solubilization of the drugs. For the poorly water-soluble drugs with poor membrane permeability, which belong to BCS class IV,

formulation strategies can do little to improve their absorption due to the limited membrane permeability; the best solution to improve their bioavailability is to go back to the lead optimization phase of drug discovery and modify their structures to obtain the appropriate physicochemical properties (4). Amorphous solid dispersion is an increasingly important formulation approach to improve the dissolution rate and apparent solubility of poorly water soluble compounds (6, 7, and 8). A successful solid dispersion formulation should be easily processable to final dosage form and remain chemically as well as physically stable upon storage. Identification of appropriate formulation components is important to develop a successful amorphous solid dispersion with desired release profile. In addition, methods used to prepare amorphous solid dispersion can also influence each ofthese important properties of the dispersion.Commonly used methods for preparation of solid dispersions includes the fusion or solvent processes such as hot melt extrusion(HME) (9, 10, 11), spray drying (SD) (12,13), solvent co-precipitation (CP) (14), and supercritical fluid process (15). Solid dispersions represent a promising formulation approach for overcoming today'smajor challenge in pharmaceutical formulation development: poorly soluble and poorly permeable active pharmaceutical ingredients (APIs).

3. BACKGROUND:

I. Defining the needs:

Oral drug delivery is the simplest and easiest way of administering drugs (16, 17). Because of the greater stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms have many advantages over other types of oral dosage forms. Therefore, most of the new chemical entities (NCE) under development these days are intended to be used as a solid dosage form that originate an effective and reproducible in vivo plasma concentration after oral administration (18,19). In fact, most NCEs are poorly water soluble drugs, not well-absorbed after oral administration (19, 20), which can detract from the drug’s inherent efficacy (21–23). Moreover, most promising NCEs, despite their high permeability, are generally only absorbed in the upper small intestine, absorption being reduced significantly after the ileum, showing, therefore, that is a small absorption window (24, 25). Consequently, if these drugs are not completely released in this gastrointestinal area, they will have a low bioavailability (24, 26).

Therefore, one of the major current challenges of the pharmaceutical industry is related to strategies that improve the water solubility of drugs (21, 27, and 28). Drug release is a crucial and limiting step for oral drug bioavailability, particularly for drugs with low gastrointestinal solubility and high permeability. By improving the drug release profile of these drugs, it is possible to enhance their bioavailability and reduce side effects (27, 28, and 29).

Solid dispersions are one of the most successful strategies to improve drug release of poorly soluble drugs. These can be defined as molecular mixtures of poorly water soluble drugs in hydrophilic carriers, which present a drug release profile that is driven by the polymer properties.Solid dispersions represent a promising formulation approach for overcoming today's major challenge in pharmaceutical formulation development: poorly soluble and poorly permeable active pharmaceutical ingredients (APIs). Solid dispersions can be obtained using different processes; however, hot-melt extrusion (HME) is extremely suitable for this purpose.

II. Advantages of solid dispersions over other strategies to improve bioavailability of poorly water soluble drugs:

Improving drug bioavailability by changing their water solubility has been possible by chemical or formulation approaches (30, 31, and 32). Chemical approaches to improving bioavailability without changing the active target can be achieved by salt formation or by incorporating polar or ionizable groups in the main drug structure, resulting in the formation of a pro-drug. Solid dispersions appear to be a better approach to improve drug solubility than these techniques, because they are easier to produce and more applicable. For instance, salt formation can only be used for weakly acidic or basic drugs and not for neutral. Furthermore, it is common that salt formation does not achieve better bioavailability because of its in vivo conversion into acidic or basic forms (33, 34). Moreover, these types of approaches have the major disadvantage that the sponsoring company is obliged to perform clinical trials on these forms, since the product represents a NCE (19).

Formulation approaches include solubilization and particle size reduction techniques, and solid dispersions, among others. Solid dispersions are more acceptable to patients than solubilization products, since they give rise to solid oral dosage forms instead of liquid as solubilization products usually do (35, 36). Milling or micronization for particle size reduction is

commonly performed as approaches to improve solubility, on the basis of the increase in surface area [37, 38]. Solid dispersions are more efficient than these particle size reduction techniques, since the latter have a particle size reduction limit around 2–5 mm which frequently is not enough to improve considerably the drug solubility or drug release in the small intestine [37,36,39] and, consequently, to improve the bioavailability [35,36,40]. Moreover, solid powders with such a low particle size have poor mechanical properties, such as low flow and high adhesion, and are extremely difficult to handle (36, 38).

Literature Review:

1. **Zheng et al., 2007,** The purpose of this work was to prepare and characterize solid dispersions of nimodipine with hydroxypropyl methylcellulose (HPMC,Methocel E5), polyvinylpyrrolidone/vinyl acetate copolymer (PVP/VA, Plasdone S630®), and ethyl acrylate, methyl methacrylate polymer (Eudragit® EPO). The goal was to investigate whether the solid dispersion prepared by hot-melt extrusion can improve the dissolution rate of nimodipine.(10)

2. **Miller et al., 2007,** The purpose of this work was to study and to demonstrate a processing technique in which hot-melt extrusion (HME) is utilized to overcomelimitations such as particle aggregation, morphological instability, and poor wettability. Micronized particles of amorphousitraconazole (ITZ) stabilized with PVP or HPMC were produced and subsequently melt extruded with poloxamer 407 and PEO 200 M to deaggregate and disperse the particlesinto the hydrophilic polymer matrix. Differential scanning colorimetry, X-ray diffraction,and scanning electron microscopy were used to demonstrate that the HME process didnot alter the properties of the micronized particles. (9)

3. **Zhu et al., 2006,** Studied the influence of plasticizer level ondrug release for solid dosage forms preparedby hot-melt extrusion and film coating. The properties of two highly water-soluble compounds, diltiazem hydrochloride(DTZ) and chlorpheniramine maleate (CPM), and a poorlywater-soluble drug, indomethacin (IDM), were investigated in the melt extrudates containing either Eudragit® RSPO or Eudragit® RD 100 and triethyl citrate (TEC) as the plasticizer. (11)

4. **Sarode et al., 2013,** The purpose of this investigation was to evaluate and study the impact of solid state intermoleculardrug–polymer interactions on supersaturation. Poorly water soluble drugs Indomethacin (IND), Itraconazole (ITZ), and Griseofulvin (GSF) and hydrophilic polymers – Eudragit EPO,Eudragit L-100-55, Eudragit L-100, HPMCAS-LF, and HPMCAS-MF, Pharmacoat 603, and Kollidon VA-64 wereselected for this study. Solubility parameters calculations (SPCs), differential scanning colorimetry (DSC),and rheological analysis of drug–polymer physical mixtures (PMs) were performed. The solid dispersionswere manufactured using HME and characterized by powder X-ray diffraction (PXRD), polarized light microscopy (PLM), Fourier transform infra-red (FTIR) Spectroscopy, and dissolution study. [(41)]

5. **Takeuchi et al., 2004,** The purpose of this work was to prepare solid dispersion particles of tolbutamide (TBM) by formulating nonporous (Aerosil 200 (hydrophilic), AerosilR972(hydrophobic)) or porous (Sylysia 350 (hydrophilic), Sylophobic 200 (hydrophobic)) silica as a carrier and applying the spray-drying (SD) orevaporation (Eva) method. In the solid dispersion particles prepared by the SD method, TBM existed in a meta-stable form (Form II) irrespective of the type of silica. On the other hand, when the Eva method was used, various crystalline forms of TBM were observed in thesolid dispersion particles according to the type of silica. Polymorphs of Forms III and IV were prepared with Aerosil 200 and Aerosil R972,respectively, while crystalline Form II was obtained when either of the forms of porous silica, Sylysia 350 or Sylophobic 200, wasformulated.[(13)]

6. **Chauhan et al., 2005,** The purpose of this work was to study solid dispersions (SDs) of glibenclamide (GBM); a poorly water-soluble drug and polyglycolized glycerides (Gelucire®) with the aid of silicon dioxide (Aerosil® 200); as an adsorbent, were prepared by spray drying technique. SDs and spray dried GBM in comparison with pure GBM and corresponding physical mixtures (PMs) were initially characterized and then subjected to ageing study up to 3 months. Initial characterization of SDs and spray driedGBMby DSC and XRPD showed thatGBMwas present in its amorphous form (AGBM). Improvement in the solubility and dissolution rate was observed for all samples.[(12)]

7. **El-Gazayerly, 2000.,** The purpose of this study was to increase dissolution of tenoxicam, with commonly used excipients by coprecipitation method. The coprecipitates were prepared using the solvent evaporation method, and the ratio used was 1:3 drug to additive. The prepared coprecipitates were subjected to a dissolution study, and they were characterized using infrared (IR) and differential scanning colorimetry (DSC).[14]

8. **Moneghini et al., 2001.,** The purpose of this study was to apply the attractive technique of the supercritical fluid to the preparation of solvent-free solid dispersions. In particular, the gas antisolvent crystallization technique (GAS), using supercritical carbon dioxide as processing medium, has been considered to prepare an enhanced release dosage form for of the poorly soluble carbamazepine, employing PEG 4000 as a hydrophilic carrier.[15]

4. RATIONALES OF STUDY:

Solid dispersions are one of the most promising strategies to improve the oral bioavailability of poorly water soluble drugs. By reducing drug particle size to the absolute minimum, and hence improving drug wettability, bioavailability may be significantly improved. They are usually presented as amorphous products, mainly obtained by two major different methods, for example, melting and solvent evaporation. Recently, surfactants have been included to stabilize the formulations, thus avoiding drug recrystallization and potentiating their solubility. Solid dispersions traditionally have been used as effective methods to improve the dissolution properties and bioavailability of poorly water-soluble drugs. The aim of the present study was to improve the solubility and dissolutionrate of poorly water-soluble drugs, by a solid dispersion technique. New manufacturing processes like hot melt extrusion obtain solid dispersions which can reduce the drawbacks of the conventional processes.

5. PLAN OF WORK

5.1 Preformulation

5.1.1 APIs studies

- Description, Solubility, LOD (Loss on Drying)
- Bulk density, Assay

5.1.2 APIs studies from IP, USP and BP

- Category
- Identification Test
- Assay

5.1.3 Testing of APIs

- Polymorph- X-ray diffraction method.
- Particle size distribution- Sieve Analysis method
- LOD - Thermal gravimetric method
- Assay- HPLC
- Bulk density- Tapping method

5.1.4 Excipients Interaction Studies

- Drug excipients interaction - Differential scanning colorimetry

5.2 Formulation

- Evaluation of solid dispersion formulations by hot melt extrusion processing
- Suitable formulation from solid dispersion

5.3 Characterization of formulation

5.3.1 Physical characterization

- Powder X-ray diffraction (PXRD)
- Microscopy
- Rheological evaluation

5.3.2 Chemical characterization

- Fourier transformed infra-red (FTIR) spectroscopy
- Thermal analysis

5.4Evaluation of formulation

- Physical appearance, colour
- Flow property- Carr's Compressibility and Angle of repose.
- Assay- HPLC Method
- Dissolution- Dissolution test apparatus
- Moisture content by KF

5.5 Stability Studies

- Schedule of Stability study, No. of Station, Storage condition

  Condition- Accelerated stability studies for 0,1,3,6 months by using ICH guideline
- Test during stability studies

5.6 In vivo studies

- Bioequivalence studies against conventional product.

6. DURATION OF WORK:

Sr.	WORK	PERIOD
1	Literature review	6 Months
2	Selection and procurement of required drugs and excipients	4 Months
3	Characterization of procured drugs and excipients.	4 Months
4	Pre-formulations Study	4 Months
5	Formulation of solid dispersions	8 Months
6	Characterization of solid dispersion	6 Months
7	Evaluation of solid dispersion formulation	4 Months
	Total duration of project	**36 Months**

7. RESEARCHOUTCOME:

Solid dispersion techniques are increasingly attractive process for the manufacture of various drug delivery systems. The literature published in this field so far reveals many interesting aspects such as fast dispersing systems, floating systems, complex formation within the melt and nano-particle engineering combined with melt extrusion technology. Many of the pharmaceutical products preparedutilizing this technique have been approved. The drug being embedded in the carrier matrices as a solid dispersion/solution may allow for dissolution rate improvement.

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